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Review

Neurophysiological and Vascular Mechanisms of Action of Serotoninergic Drugs for Abortive Migraine Treatment

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Migraine is a form of primary headache that affects at least 10% of the world's population. In addition to advising patients to modify their lifestyles, the management of migraine includes terminating ongoing attacks and/or preventing attacks from occurring. Pharmacological agents of both nonspecific (for example, non-narcotic analgesics), and specific actions can be used for the abortive treatment of this form of headache. Specific treatments include, in particular, serotoninergic agents: triptans (selective 5-HT1B/1D receptor agonists), ditans (selective 5-HT1F-mimetics) and ergot alkaloids (non-selective modulators of various subtypes of 5-HT receptor). This review presents the currently known results from many basic and applied studies of drugs from these groups, identifying the neuronal and vascular components of their anti-migraine pharmacodynamics. Significant quantities of these data were obtained in vivo in a variety of experimental models of migraine based on the trigeminovascular theory of its pathogenesis. Other information is based on ex vivo work on isolated tissues and cell cultures. Analysis of results from these studies yielded evidence in favor of the notion that the anti-migraine potential of members of all of these pharmacological classes is mediated by similar mechanisms, whereby neurotropic activity dominates over direct intervention in vascular tone. Special attention is paid to uncertain and controversial issues in this area, whose successful solution is key to further progress in the pharmacotherapy of migraine.

Keywords: migraine, headache, triptans, lasmiditan, ergot alkaloids, serotonin, neurophysiology, mechanism of action, vasoconstriction.

Abbreviations: i.v., s.c. – intravenous, subcutaneous; GABA – gamma-aminobutyric acid; HA – headache; BBB – blood–brain barrier; DHE – dihydroergotamine; CHA – cluster headache; MOH – medication overuse headache; MB – mitochondrial biogenesis; CSD – cortical spreading depression; STN – spinal trigeminal nucleus; TVS – trigeminovascular system; TG – trigeminal ganglion; DM – dura mater; TCC – trigeminocervical complex; CNS – central nervous system; 5-HT (5-hydroxytryptamine) – serotonin; CGRP – calcitonin gene-related peptide; L-NAME – N(ω) Nitro-L-arginine methyl ester; NKA – neurokinin A; NO – nitric oxide; NOS – nitric oxide synthase; PACAP – Pituitary adenylate cyclase-activating polypeptide; SP – substance P.

Introduction. The most prevalent of all pain syndromes is headache (HA), which is understood as any unpleasant sensation above the orbitomeatal line and/or nuchal crest. The *International Classification of Headache Disorders* distinguishes between primary and secondary headache; the latter are a symptom of some independent disease, i.e., there is an objective reason for their occurrence. Primary headaches, which include tension-type headache, migraine, trigeminal autonomic cephalgias, including cluster headache (CHA), and so-called "other primary headaches," are all idiopathic disorders, do not have a specific etiology, and are diagnosed on the basis of the clinical picture and exclusion of other conditions able to cause similar symptoms [2, 107].

According to the definition used by Russian experts, "migraine is a primary form of headache manifest as attacks of pulsating unilateral headache lasting 4–72 hours accompanied by increased sensitivity to light, sound, nausea, and/or vomiting" [1]. From the points of view of the prevalences of different headaches, the severity of cumulative damage to health, the clarity and diversity of the clinical manifestations, the extent of concomitant social maladjustment, and the magnitude of relative economic losses, as well as the

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level of familiarity among the population and the research effort made, migraine is undoubtedly the most notable form of all the primary headaches.

Pathophysiology of Migraine. In 1979, a group of American researchers led by Michael Moskowitz postulated a theory of migraine pathogenesis, subsequently termed the trigeminovascular theory, the essence of which is that this type of headache is a neurovascular pathology [161]. This hypothesis holds that the formation of this headache is based on disruption of the interaction between extra- and intracranial vessels, the trigeminal nerve, and CNS structures anatomically connected into a functionally unified trigeminovascular system (TVS) and forming the ascending trigeminothalamocortical pathway, which is under neurohumoral control. A migraine attack occurs as a result of trigeminovascular activation occurring spontaneously or in response to a variety of exo- and/or endogenous triggers [132] in conditions of congenital or acquired deficiency of descending antinociceptive influences, leading to cranial vasodilation and the development of aseptic neurogenic inflammation of the meningeal vessels and perivasal tissues due to the antidromic release of various vasoactive substances, for example, calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating peptide (PACAP), neurokinin A (NKA), nitric oxide (NO), and substance P (SP), from the peripheral terminals of trigeminal afferents. In conditions of meningovasculitis, the perivascular fibers of the trigeminal nerve undergo orthodromic stimulation and sensitization; these fibers carry nociceptive information from the meninges and cranial vessels to the spinal nucleus of the trigeminal nerve (STN), where it undergoes initial processing and is then transmitted on to overlying CNS structures. The axons of STN neurons, whose caudal subnucleus (the trigeminal nucleus caudalis, Sp5C) taken together with the ipsilateral dorsal horn of the upper cervical segments of the spinal cord, is regarded as a single neuroanatomical formation termed the "trigeminocervical complex" (TCC), form ascending connections with a number of subcortical areas of the brain, including the thalamus, which serves as the last relay center for transmission of pain signals to the somatosensory areas of the cortex [2, 74, 91, 169]. The questions of what exactly leads to the primary antidromic activation of the sensory endings of the trigeminal nerve and how it does so remain open and are the subject of continuing debate [65].

Since its inception, the classical presentation of the trigeminovascular theory has constantly been subject to significant modifications in the light of new clinical and experimental observations [2, 11, 102]. In particular, the modern understanding is that the mediators present in primary trigeminal neurons have unequal roles in the genesis of migraine – CGRP is currently seen as being in first place. This substance is regarded as the main "pro-migraine" molecule, other neurotransmitters such as glutamate, NO, SP, etc., being in its shadow [46, 70, 71, 122]. The only neuropeptide that might be seen in the foreseeable future as able to compete with CGRP as the presumptive main inducer of migraine is PACAP, which has been receiving steadily increasing attention over the past 10 years [100, 204]. As the C fibers of trigeminal nerve afferents are the main reservoir of CGRP, antidromic activation of these fibers – for example, by passage of a wave of cortical spreading depression (CSD) [156] or changes in the function of the hypothalamus [102, 153] – may be accompanied by release of CGRP (both from nerve endings and from any non-myelinated area of the neuron membrane) and increases in the orthodromic excitability of CGRP receptor-expressing Aδ fibers, such that we can speculate about the likely distribution of functions of C- and Aδ fibers within the boundaries of the TVS and their importance in the initiation and development of headache attacks [72, 75]. It is of note that this mechanism can occur both with and without involving the pial and dural arteries, which is important in the light of the extremely contradictory views which have developed on the roles of intra- and extracranial vessels in the pathogenesis of migraine [2]. Thus, some researchers have questioned the importance and sometimes even the very existence of aseptic neurogenic inflammation of the meningeal vessels; in any case, if this process does in fact occur, it can hardly be an absolute requirement for the development of a migraine attack. It has been suggested that dilation of cranial vessels is not an obligatory or consistent component in the pathogenesis of migraine, just as vasoconstriction is not a necessary component of the successful treatment of attacks; if cerebral vasodilation is observed during a migraine attack, it is often regarded as no more than an epiphenomenon of activation of the trigeminal-parasympathetic reflex [32, 91].

Nonetheless, despite the inconsistency and uncertainty of modern concepts of the roles of neurogenic vasculitis and vasodilation, most researchers remain unanimous that the main sources of pain in migraine are the meningeal vessels, including the sinuses of the dura mater (DM) and the large cerebral and extracranial arteries [11, 18, 102]. The cellular elements of vascular walls, along with meningeal immune cells and perivascular sensory and autonomic nerve fibers, form a functionally unified continuum involved in the initiation and progression of migraine attacks due to the release of various biologically active substances [12, 24, 41, 70, 100, 143, 190, 205].

Thus, migraine can be regarded as a complex disorder of sensory processing in the CNS associated with neurovascular disturbance in the periphery, though the cause-and-effect relationship between central and peripheral pathophysiological events remains unclear [65]. Neurovascular dysfunction, coupled with an increase in nociceptive traffic on the background of a defect in the control exerted by brainstem and cortical structures, which are often referred to as *migraine generators* [193], is accompanied by the development of peripheral and central sensitization of the neuronal elements of the trigemino-thalamo-cortical pathway, which is clinically apparent as a characteristic pain syndrome, with

cutaneous allodynia, photo-/phono-/osmophobia, and concomitant autonomic symptoms [2, 11, 46, 74, 91, 102, 169].

The Treatment of Migraine. In addition to lifestyle modification advice for patients, the management of migraine involves terminating ongoing attacks (abortive treatment) and/or preventing attacks from occurring. Selection of one or another tactic depends on the clinical picture of the disease (number of days with headache per month, intensity of attacks, severity of concomitant symptoms, degree of maladjustment, etc.), the presence of comorbid pathologies, the tolerability and efficacies of prescribed drugs, as well as patients' treatment compliance [1, 2]. It is of note that despite the deservedly growing popularity of non-pharmacological treatment methods, especially various methods of non-invasive electrical neurostimulation (for example, trigeminal, vagus, and occipital nerve stimulation) [4, 81, 214], the pharmacological approach naturally retains its position as the main approach.

The goals of abortive therapy are to completely terminate a headache attack (or at least reduce its intensity and duration), to reduce the likelihood of relapse of a migraine attack, to restore the patient's general condition, and to eliminate headache-associated symptoms such as nausea, vomiting, photophobia, etc.; pharmacological agents with both nonspecific and specific actions can be used [1, 2, 213, 218].

Non-specific drugs have potential for non-selective analgesia and are able to relieve pain of various origins, for example, pain due to injury, neoplasms, or inflammation, and with almost any localization, not being restricted to the head (these agents are non-steroidal anti-inflammatory drugs, anesthetics, and, to some extent, glucocorticosteroids); or they can have no notable analgesic activity (dopaminolytics, magnesium salts, GABA modulators).

Apart from ergot alkaloids, all drugs with specific actions – the so-called triptans, ditans, and gepants – were specifically created for the treatment of migraine attacks and are currently used almost exclusively for this indication (triptans and dihydroergotamine are also used in abortive therapy for CHA). Neurochemical activity profiles allow these drugs to be divided into two unequal pharmacological groups: drugs selectively blocking CGRP receptors (gepants) and serotoninergic drugs of varying degrees of selectivity of action (triptans, ditans, and ergot alkaloids). The present review addresses members of the second group and notes that gepants require separate consideration.

Triptans. Currently, selective serotonin (5-HT) 1B/1D receptor agonists – triptans – are among of the most studied and frequently used drugs for the relief of migraine attacks and CHA; their efficacy has been confirmed by results from numerous clinical studies [22, 213, 218]. Historically, sumatriptan was the first triptan, whose introduction in 1991 was an undoubted breakthrough in the abortive treatment of migraine [119, 226]. As of March 2023, seven members of the triptan group are used around the world, of which sumatriptan [246], zolmitriptan [242], and eletriptan [247] are registered in Russia as tablets for oral administration (all drugs) and nasal spray (zolmitriptan). In other countries, naratriptan, rizatriptan, almotriptan, and frovatriptan are available as tablets; sumatriptan is also available as solution for subcutaneous (s.c.) administration and as spray or powder for intranasal use; work continues on the creation of innovative dosage forms and delivery methods for triptans, which will improve their pharmacokinetic characteristics and increase efficacy and safety [152, 217, 236].

Triptans do not have an internal classification, though they are sometimes divided into two arbitrary groups: drugs with rapid onset of action after oral administration (less than 60 min – sumatriptan, zolmitriptan, rizatriptan, and eletriptan) and slow onset of action (more than 60 min – naratriptan, frovatriptan, and almotriptan); the clinical significance of this kind of separation is questionable. Attempts have also been made to divide triptans into two generations, the first including sumatriptan and the second all other drugs [118, 172, 186, 226].

Triptans are structurally similar to serotonin: their molecular structure is based on an indole core to which a variety of radicals are attached in positions 3 and 5 to determine the pharmacokinetic characteristics of individual drugs [213, 226]. In particular, triptans are discriminated by their lipophilicity (low for sumatriptan and frovatriptan, medium for zolmirtriptan, rizatriptan, and almotriptan, high for eletriptan and naratriptan) [138, 172, 186], which can in theory affect the balance of the peripheral and central pharmacodynamic effects but is unlikely to have any clinical significance when using oral forms [82].

The mechanism of the anticephalgic action of triptans is associated with activation of the corresponding subclasses of 5-HT1 receptors and consists of vascular and neuronal components [118, 172, 212, 226]. Before reviewing this in detail, it should be noted that metabotropic Gi/Go-protein-coupled 5-HT1B and 5-HT1D receptors are widely distributed in various tissues, including the neuroanatomical structures involved in the genesis of migraine [2, 15, 87, 144, 169], and mediate the participation of serotonin in nociceptive processing [14, 50, 108, 209].

Pharmacodynamics: direct vasotropic effect. As 5-HT1B receptors are expressed on smooth muscle and endothelial cells in the walls of arteries in the head [144] and given that their activation leads to direct and indirect vasoconstriction due to contraction of smooth muscle elements and inhibition of endothelial NO synthase (NOS) respectively, it is generally accepted that the vascular component of the antimigraine effect of triptans lies in the 5-HT1B-mediated restoration of the tone of dilated cranial arteries; more precisely, triptans prevent their excessive dilatation [15, 18, 138, 172, 174, 210]. This property is often seen as a vasoconstrictor effect, though this is not entirely correct as vasoconstriction itself has been demonstrated mainly in experiments on arteries isolated from different anatomical regions [29, 76, 123, 146, 147, 151, 154, 179, 184, 185, 192, 196] and veins [47, 48,

126, 166] from humans and animals. The reductions in carotid blood flow described with sumatriptan [42, 43, 101, 154, 164, 165, 185], eletriptan [101], and naratriptan [89] in in vivo experiments also cannot be regarded unambiguously as a consequence or surrogate of vasoconstriction, though studies in anesthetized dogs showed that sumatriptan produced a dose-dependent decrease in the diameter of the common carotid and coronary arteries [185]. It is interesting to note that the presence of intact endothelium significantly attenuated sumatriptan-induced contraction of isolated rabbit basilar artery and saphenous vein (which is regarded as a model for human coronary arteries), while removal of the endothelium or inhibition of NOS with L-NAME enhanced the contractile effect of the drug [21]. Sumatriptan only partially suppressed the dilatation reaction of meningeal vessels in response to intracarotid administration of sodium nitroprusside in experiments on rats, this effect being transient and disappearing with continued infusion of the NO donor [6]. Magnetic resonance angiography studies in healthy volunteers indicated that sumatriptan did not prevent dilatation of the superficial temporal, middle meningeal, or middle cerebral arteries induced by infusion of PACAP-38, though it restored the tone of the first two of these vessels when given late, i.e., 90 min after cessation of neuropeptide administration [84]. This same agent did not impair shunting along dural arteriovenous anastomoses in pigs [63], while Doppler ultrasound investigations found that it either did not alter blood flow velocity in the middle cerebral, basilar, common carotid, or external carotid arteries [64] or significantly increased it in the middle cerebral and internal carotid arteries in individuals with migraine [39, 64, 215]. Rizatriptan given orally to relieve migraine attacks had no effect on blood flow velocity in either of the middle cerebral arteries [97]. Moreover, ex vivo and in vivo studies have even demonstrated vasodilatory effects with triptans, indicating the dose-dependence and species-specificity of their vascular actions, for example, in relation to humans and rodents [77, 137, 192]. At the same time, potential vasoconstrictor properties determine the risks of using triptans in people with cardiovascular diseases [2, 137, 146, 147, 186], and this is reflected in the list of contraindications to their use [242, 246, 247].

Pharmacodynamics: neurotropic effects. *Peripheral neurovascular effect*. The neuronal component of the pharmacodynamics of triptans at the level of the peripheral part of the TVS is represented by inhibition of the release of neuropeptides from the sensory endings of the trigeminal nerve and blockade of nociceptive information in the STN, which is associated with the effects of activation of both 5-HT1B and 5-HT1D receptors [66, 87, 89, 138, 159, 210], the latter often being given the leading role [22, 172, 178]. Receptors of these subclasses are known to be located on the bodies and processes of trigeminal ganglion (TG) neurons, which are predominantly immunopositive for CGRP, SP, and NOS; these receptors are probably also located directly on the projection cells of the STN [9, 45, 73, 105, 117, 144, 145].

Activation of peripheral presynaptic 5-HT1B/1D receptors leads to inhibition of the release of CGRP and other transmitters from the perivascular terminals of predominantly trigeminal C fibers, preventing the development of cranial vasodilation, probably accompanied by an increase in vascular permeability, activation of dural immune cells, and orthodromic excitation mainly of Aδ nociceptors [46, 87, 102].

Thus, experiments on rodents using intravital microscopy showed that sumatriptan [137, 229] and rizatriptan [230, 231] produced dose-dependent suppression of neurogenic dural vasodilation induced by electrical stimulation of trigeminal afferents through the so-called closed cranial window. Given that neurogenic dural vasodilation was also blocked by the selective 5-HT1D agonist PNU-142633 and that neither triptan had any effect on CGRP-induced dilatation of the meningeal arteries, the results of these experiments indicate that, in conditions of TVS activation, 5-HT1B/1D agonists have a mainly neuronal effect at the neurovascular synapse level, mediated primarily via presynaptic 5-HT1D receptors, while their direct vasotropic effect is of quite minor importance, as triptans were unable to prevent CGRP-induced dilatation of meningeal arteries by activating vascular 5-HT1B receptors. Sumatriptan [36, 38, 126, 154, 197], zolmitriptan [126, 151], rizatriptan [126, 231], naratriptan [126], and eletriptan [101] also inhibited extravasation of plasma proteins into the DM provoked by electrical stimulation of the TG. Experiments on cats using laser Doppler flowmeter showed that sumatriptan reduced the magnitude of an increase in cerebral meningeal microcirculation induced by this type of stimulation [90].

Prior intravenous (i.v.) administration of sumatriptan, significantly reduced the number of dural mast cells (mastocytes) undergoing degranulation in response to ipsilateral electrical stimulation of the TG in rats and also decreased the morphological signs of endothelial cell activation and platelet aggregation in postcapillary venules in the DM [35]. These data, obtained more than 30 years ago, demonstrate an important component of the pharmacodynamics of triptans: firstly, mast cell mediators are activators and sensitizers of trigeminal afferents, which is also reflected in the subsequent increase in c-fos reactivity of TCC neurons [141, 235], and secondly, our understanding of the major roles of meningeal immune cells, i.e., local neuro-immuno-vascular interactions, and neuroinflammation in the pathobiology of migraine expands year on year [12, 24, 41, 70, 143, 190, 205].

Effects at the level of the TG and STN: results of electrophysiological studies. In turn, the effect of activation of 5-HT1B/1D receptors located presynaptically on the central processes of neurons of the TG consists of inhibition of the release of glutamate, SP, CGRP, and NO from nerve endings, which evidently inhibits trigeminovascular sensory transmission at the level of the STN. Studies in animals using an electrophysiological model of trigemino-durovascular nociception, based on extracellular microelectrode

recording of the spike activity of meningeal sensory neurons of the trigeminothalamic pathway [3], showed that i.v. administration of sumatriptan [110, 131], zolmitriptan [92, 151, 52], rizatriptan [51], and naratriptan [19, 53, 89, 93, 111, 171] was accompanied by suppression of the responses of trigeminocervical neurons to electrical stimulation of the DM; some early studies found that the effect of naratriptan was blocked by both 5HT1B and 5-HT1D antagonists. Other data indicate that the involvement of neuronal 5-HT1B receptors in the inhibition of trigeminal nociceptive transmission is insignificant. In any case, a study in rats found that i.v. administration of the selective 5-HT1B agonist CP-93,129 did not disrupt the activity of TCC neurons induced by electrical stimulation of the middle meningeal artery [52]. Two of the studies listed above assessed the effects of naratriptan on the frequency of TCC cell spontaneous discharges: there was either no change [53] or inhibition [171]; in turn, sumatriptan had no effect on background neuronal activity [110].

It is important to take account of the fact that these models, with systemic administration of drugs without sensitization of cells, cannot accurately determine the neuroanatomical level of inhibition of evoked activity: a substance has equal probabilities of binding to both pre- and postsynaptic receptors within the STN or even suppressing the excitability of primary afferent neurons of the TG. Experiments using local microiontophoretic delivery of drugs to the TCC helped verify that the site of action of triptans is central. Given by this method, sumatriptan, zolmitriptan [206], and naratriptan [25, 66] have been shown to suppress the responses of neurons in this structure to stimulation of the DM; the effect of the latter was blocked by 5-HT1B/1D antagonists, while sumatriptan with zolmitriptan also inhibited background spike activity. In cats, iontophoresis of eletriptan produced a 5-HT1B/1D-dependent reversal of the increase in spontaneous spike frequency of dura-sensitive TCC neurons induced by intracarotid administration of nitroglycerin, a recognized activator of the TVS [139]. In addition, experiments on cats showed that sumatriptan reduced the increase in TCC cell firing induced by local administration of NMDA agonists [88], which may indicate that this drug has a postsynaptic effect. Electron microscopy data demonstrating both pre- and postsynaptic localizations of 5-HT1D receptors in the TCC in rats provide partial support for this suggestion [148].

However, the proposals made in early articles on the central mechanism of action of triptans directly at the level of the bodies of TCC projection neurons [88], i.e., by activating 5-HT1 receptors expressed on their membranes, were not confirmed experimentally in later studies performed in the same electrophysiological model of trigemino-durovascular nociception in which the excitation of sensitized rather than naïve neurons was assessed. In particular, experiments on rats showed that i.v. sumatriptan could prevent but not terminate established TCC cell sensitization [31, 142] induced by dural application of a so-called "inflammatory soup" (a mixture of bradykinin, serotonin, histamine, and prostaglandin E2, pH < 7), which is widely used in experimental cephalgology [180]. Sumatriptan had no effect on the sensitization of TG neurons [142], which led researchers to the conclusion that the neuronal mechanism of action of triptans consists of 5-HT1B/1D-mediated presynaptic inhibition of nociceptive traffic at the first synapse of the trigeminothalamo-cortical pathway by suppressing mediator release from the terminals of the central processes of TG cells. The results of these experimental studies were consistent with clinical observations reported by essentially the same team of authors, which demonstrated the extremely low efficacy of triptans in relieving migraine attacks with cutaneous allodynia, which is a clinical correlate of central sensitization [30].

However, even more recent experiments on isolated rat TG neurons showed that sumatriptan suppressed calcium currents, increased potassium release [106], inhibited the functioning of TRPV1 channels [80], and also produced 5-HT1D-dependent neutralization of the excitatory effect of proinflammatory mediators [106], suppressing the activity of acid-sensitive ion channels (ASICs), which play a significant role in the development of peripheral sensitization [99]. I.v. administration of naratriptan to rats reversed the neurophysiological manifestations of sensitization of TCC neurons induced by nitroglycerin, i.e., it reduced their spontaneous discharge frequency, suppressed Aδ- and C- responses to electrical stimulation of the DM, and decreased the sensitivity of the receptive fields of the facial skin to multimodal mechanical stimulation [5]. The results of this study refuted previous conclusions that it is impossible to terminate established central sensitization with triptans [31, 142] and support the occurrence of the mechanism described above, i.e., postsynaptic inhibition of TCC cell activity [88]. Significant methodological differences in these studies, such as the principles of induction of sensitization and the triptans studied, do not allow unambiguous conclusions to be drawn regarding the correctness of the various views. Nonetheless, the conclusions drawn by Ackerman et al. [5] are supported by the fact that i.p. sumatriptan in mice neutralized CSD-induced signs of established central sensitization, i.e., facial thermal hyperalgesia, photophobia, and decreased motor activity [208]. In any case, the clinical and therapeutic interpretation of the overall experimental data is that administration of triptans at the very beginning of a migraine attack, if possible, is advised, i.e., before persistent sensitization of 1–3-order trigeminovascular neurons develops and the full-blown attack unfolds [2, 213]. Ex vivo [106] and in vivo [33, 207] experiments showed that sumatriptan produced transient increases in the excitability of dural afferents in rats, which is consistent with clinical observations showing that transient increases in headache could occur in individuals with migraine attacks after taking triptans.

Effects on CGRP exocytosis and neuron metabolism. Results from biochemical, morphological, and immuno-

histochemical studies supplement our understanding of the neuronal mechanisms of the anti-migraine action of triptans, which are based on inhibition of exocytosis of biologically active substances from the terminals of the peripheral and central processes of TG neurons. Thus, in vivo studies showed that i.v. avitriptan blocked the release of CGRP into blood flow through the jugular vein provoked by stimulation of the DM [134], while zolmitriptan had a similar effect, the only difference being that the TG was stimulated [151]. In rats, i.v. sumatriptan prevented exocytosis of CGRP from dural perivascular terminals induced by electrical stimulation of TG [136] and increased levels of this peptide in blood samples obtained from the superior sagittal sinus [34]. In cats, sumatriptan reduced the CGRP concentration in external jugular vein blood, which was increased on the side of TG stimulation [90]. In a clinical study, sumatriptan given as nasal spray or s.c. decreased plasma CGRP concentrations, which paralleled a decrease in headache intensity during nitroglycerin-induced or spontaneous migraine attacks [90, 127]. This same drug given parenterally to healthy volunteers suppressed the increase in local blood flow in the skin of the forehead after application of capsaicin; the authors linked this effect with the ability of the drug to inhibit CGRP release from capsaicin-sensitive cutaneous terminals of the trigeminal nerve [121].

Studies in cultured rat TG neurons found that sumatriptan suppressed CGRP secretion stimulated by depolarization or a proinflammatory agents, with no effect on basal secretion [69]. In isolated rat tissues, the same drug inhibited potassium chloride-induced CGRP release: by 31% in the DM, by 44% in the TG, and by 56% in the STN; this effect was reversed by the 5-HT1B/1D antagonist GR127395 and partially reproduced by 5-HT1D but not by 5-HT1B-agonists [9]. Sumatriptan had similar actions in ex vivo DM, TG, and STN preparations from mice [137].

In rats and mice, systemic sumatriptan prevented, including in a 5-HT1B-dependent manner, induction of c-fos expression in neurons of the caudal portion of the STN after intracisternal administration of capsaicin, carrageenan, or autologous blood, indicating suppression of neuronal metabolism [157–159, 170]. Rat experiments showed that electrical stimulation of the TG induced morphological changes in CGRP-immunoreactive nerve fibers in the DM and contributed to an increase in the number of neurons expressing c-jun and c-fos proteins in the TCC; eletriptan neutralized these changes while simultaneously disrupting CGRP expression in the perikarya of TG cells [135]. On the basis of the concept that the increase in metabolic activity in the TCC induced by electrical stimulation of the TG should be accompanied by an increase in local blood flow in this complex, McCall demonstrated this in acute experiments on cats using a laser Doppler flowmeter, finding that i.v. sumatriptan significantly reversed these microcirculatory changes [155].

Interestingly, studies in cats showed that eletriptan and zolmitriptan, but not sumatriptan, inhibited the accumulation of c-fos proteins in the TCC induced by electrical stimulation of the superior sagittal sinus; the authors explained this observation in terms of differences in the lipophilicity of the drugs tested and, accordingly, their ability to cross the blood-brain barrier (BBB) and have direct inhibitory actions on cells within this nucleus [113, 159]. A similar result was obtained in experiments on rats, where i.v. sumatriptan also did not prevent the expression of c-fos proteins induced by electrical stimulation of the TG [136]. It is relevant to note that the ability of triptans to penetrate the CNS was also addressed in an electrophysiological study, which showed that i.v. sumatriptan suppresses the responses of TCC neurons only after damage to the BBB by infusion of a hyperosmolar solution of mannitol [131]. However, the correctness of these data, as well as the conclusions drawn from them, were thrown into doubt by the results of a later study, which showed that i.v. sumatriptan inhibited induced neuronal activity in the TCC without damaging the BBB [110]. Studies on vagosympathectomized dogs showed that sumatriptan produced 5-HT1B-reversible and 5-HT1D-independent inhibition of an increase in external carotid artery blood flow induced by intracarotid infusion of capsaicin but not α-CGRP or acetylcholine, and only when given intrathecally, but not i.v.; in turn, lipophilic donitriptan exhibited a similar effect when given i.v. [164, 165]. In any case, crossing of the BBB by sumatriptan remains under scientific discussion, as do the completeness of its central neuronal effects and the issue of disruption of the BBB during migraine attacks [186].

Effects at the supraspinal level. The wide representation of 5-HT1 receptors in suprasegmental structures, including those directly related to the pathophysiology of HA [15], identifies additional points for the actions of triptans [138, 186]. Positron emission tomography data have confirmed the existence of binding sites for sumatriptan [59] and zolmitriptan [219], i.e., 5-HT1B receptors in the supraspinal regions of the CNS, in people with migraine. S.c. sumatriptan, in parallel with relieving HA, normalized the rate of serotonin synthesis in the brain, which is increased in migraine attacks [188]. In rats, naratriptan given i.v. and by local microiontophoretic administration 5-HT1B/1D-reversibly decreased the activity of meningeal-sensitive neurons in the ventral posteromedial nucleus of the thalamus (so-called third-order trigeminovascular neurons) induced by electrical stimulation of the DM or local administration of glutamate, thus interrupting the flow of sensory information to the cortex [198]. In addition, the drug increased the activity of inhibitory neurons in the structures of the endogenous antinociceptive system projecting to the STN. In particular, microinjections of naratriptan into the ventrolateral region of the periaqueductal gray matter in rats [16] or the parvocellular zone of the paraventricular nucleus of the hypothalamus [183] were accompanied by decreases in the background activity of TCC neurons and reductions in their responses to stimulation of the DM. I.v. naratriptan in rats

reduced the frequency of *on* cell discharges and increased the spike activity of *off* cells in the nucleus raphe magnus, thus reproducing the similar effect of morphine [78].

In turn, in vitro experiments have shown that sumatriptan produces 5-HT1B/1D-dependent inhibition of both GABAergic and glutamatergic synaptic transmission in the periaqueductal gray matter, which ultimately also leads to increases in the top-down inhibitory effects of this structure on trigeminal nociceptive traffic [124]. The same drug produced 5-HT1B-reversible presynaptic inhibition of glutamatergic transmission in sections of the bed nucleus of the stria terminalis of rats [98], which plays an important role in controlling autonomic, neuroendocrine, and behavioral responses to stress stimuli [104]. This nucleus is known to be involved in the pathogenesis of anxiety and depressive conditions, which often develop on the background of chronic pain syndromes [233], including migraine [67, 130], and can also take part in inducing migraine attacks by initiating the activation of meningeal nociceptors mediated by parasympathetic neurons of the superior salivary nucleus and pterygopalatine ganglion [2, 32].

Mechanism of the antiemetic action of triptans. One additional and useful feature of the pharmacodynamics of triptans is their ability to suppress nausea and vomiting, i.e., autonomic gastrointestinal symptoms associated with HA, which occur in up to 70% of patients at the main stage of a migraine attack [2]. It has been suggested that these drugs restore the normal motility of the gastrointestinal tract, though the detailed mechanisms of this effect reman unclear [44]. Results from a study in awake dogs led to the suggestion that triptans may enhance postprandial gastric accommodation and eliminate early satiety: this suggests a possible therapeutic potential for functional dyspepsia [58, 160], but does not explain the antiemetic effect in migraine. Furthermore, sumatriptan significantly inhibited gastric emptying of liquid food in healthy individuals [189], suggesting that the gastrokinetic effect of triptans is nosospecific. In any case, cat experiments showed that electrical stimulation of the superior sagittal sinus increased spike activity in neurons in the solitary tract nucleus, which was eliminated in a 5-HT1B/1D-reversible manner by microiontophoretic administration of eletriptan and naratriptan. Given the role of this nucleus in the genesis of nausea and vomiting [112], the results of this study may explain both the mechanism of development of these symptoms during migraine attacks and the efficacy of triptans in eliminating them [115]. Interestingly, i.v. sumatriptan did not affect c-fos expression in the solitary tract nucleus induced in rats by introduction of autologous blood into the cisterna magna [170]. However, given the possible connection between nociception and vomiting [140], there is the logical notion that the antiemetic effect of triptans could be a simple consequence of their analgesic effect on the "no headache – no vomiting" principle [138].

Triptans and drug abuse. Overuse of triptans (taken for 10 or more days a month for more than three months) can lead to the formation of secondary medication overuse headache (MOH), which requires separate treatment [1, 2]. The pathogenesis of MOH is not clear, though rat experiments showed that long-term or repeated administration of sumatriptan and naratriptan causes cutaneous tactile allodynia, persistent increases in CGRP content in dural afferents after drug withdrawal, and an increase in the expression of neuronal NOS in these afferents. The authors defined these changes as "triptan-induced latent sensitization", which leads to a critical increase in sensitivity to migraine triggers and may be the neurobiological basis of the development of MOH [56, 57]. Subsequent data demonstrated the role of Nav1.9 channels in the pathogenesis of triptan-induced MOH, as mediators of the excitatory effect of NO on dural afferents (apparent as increased secretion of CGRP, meningeal vasodilation, and mast cell degranulation), whose mediators in turn potentiated the function of Nav1.9 channels, increasing inflammation and nociceptive signaling [27]. In the light of these data, the development of the dual-action agent NXN-188, which combines the properties of a 5-HT1B/1D agonist and a neuronal NOS inhibitor, looks promising [13]; unfortunately, despite relatively positive results from experimental and clinical studies [20, 176, 226], research on this substance is currently suspended.

Triptans outside migraine. The pharmacodynamics of triptans continue to determine the limits of their clinical applications solely as drugs for the relief of migraine attacks or CHA. Occasional data have been reported on the efficacies of naratriptan [28] and sumatriptan [8] for post-puncture HA after spinal anesthesia. Clinical observations in small cohorts have indicated that s.c. [128, 129] and intranasal [199] sumatriptan may be useful for pain relief in trigeminal neuralgia. A single-center randomized controlled trial found that s.c. sumatriptan was associated with improved quality of recovery and reductions in HA after microvascular decompression of cranial nerves in patients with trigeminal neuralgia or hemifacial spasm [220]. Experimental studies in the 1990s often emphasized that the neurophysiological effects of triptans occurred exclusively within the boundaries of the TVS in its classical sense. For example, sumatriptan blocked neurogenic leakage of plasma proteins in rats and guinea pigs exclusively in the DM, but not in extracranial tissues [36–38]. Naratriptan inhibited the responses of TCC neurons to electrical and mechanical stimulation of the DM and facial skin in rats, but had no effect on the activity of dorsal horn cells of the spinal cord induced by nociceptive mechanical stimulation of the hindpaw [53]. Furthermore, i.v. sumatriptan did not prevent c-fos expression in TCC induced by application of formalin to the nasal mucosa in rats; the authors speculated about the supposed "tissue dependence" of the action of this substance, hinting at its efficacy in the case of induction of c-fos reactivity in the TCC, exclusively during meningeal stimulation [170]. Lambert's 2005 review emphasized that "Naratriptan and other successful 5HT1B/1D receptor-acti-

vating antimigraine agents are not analgesics in the normal sense of the word and have little effect on non-craniovascular pain" [138].

However, results from immunohistochemical experiments on of 5-HT1B/1D/1F receptors in the primary afferent neurons of the trigeminal and spinal ganglia led to the tentative suggestion that "triptans are theoretically able to bind to receptors at each level of the peripheral neuraxis without any apparent anatomical preference for the head" [45]. In fact, results from numerous animal studies using a variety of experimental models have indicated that triptans, primarily sumatriptan, have analgesic activity in relation to visceral and somatic pain of extracranial localization, predominantly of inflammatory origin [40, 168, 221, 232], which is addressed in relatively great detail in a systematic review [7]. In addition, studies in a rat model of myocardial ischemia-reperfusion injury showed that sumatriptan displayed a cardioprotective effect accompanied by pronounced decreases in markers of cytolysis and inflammation and improvements in left ventricular function [195]. Sumatriptan also reversed the biochemical and pathological consequences of episodes of ischemia/reperfusion in the testis [61] and intestines [85] induced by torsion/detorsion and reversible occlusion of the superior mesenteric artery respectively. Experiments on rodents showed that this drug produced dose-dependent improvements in the taking of skin grafts [60], exhibited antiallergic and neuroprotective effects in models of ovalbumin-induced rhinitis [109] and vincristine-induced neuropathy [133], and also had an antipruritic effect in chloroquine-induced pruritis [103]. Sumatriptan had a protective effect in a rat model of acetic acid-induced colitis, decreasing the severity of intestinal pathological changes, reducing the levels of inflammatory biomarkers, and inhibiting loss of body weight [116]. In mice, this drug exhibited either biphasic [96] or inhibitory [162, 163] effects on pentylenetetrazole-induced seizures, while in rats it reduced the severity of status epilepticus induced by a lithium-pilocarpine mixture [79]. It is of note that in almost all these cases, the authors emphasized the involvement of 5-HT1B/1D receptors and the NO-cGMP signal pathway. All of these results may be contrary to our current understanding of the pharmacological and therapeutic properties of triptans, including their vasoconstrictor potential, though they suggest that the indications for their use will expand in the future.

Triptans and 5-HT1A/1F receptors. In addition to being ligands for 5-HT1B/1D receptors, triptans can also exhibit varying degrees of agonistic activity towards 5-HT1A and 5-HT1F receptors [55, 185, 186]. In particular, the suppressive action of naratriptan on TCC neuron activity evoked by stimulation of the DM [25], like its action on the glutamate-induced responses of cells of the ventral posteromedial nucleus of the thalamus [198], decreased on the background of both the 5-HT1B/1D antagonist GR127935 and the 5-HT1A blockers WAY-100635 and (S)-WAY 100135. Of interest is that the excitability of thalamic neurons was also suppressed by the 5HT1A mimetic (R)-(+)-8-(OH)-DPAT [198]. Results showing that the inhibitory effect of naratriptan on the responses of TCC neurons induced by electrical stimulation of the DM was partially maintained after blockade of both 5-HT1B and 5-HT1D receptors, while the 5-HT1F agonist LY344864 had a similar inhibitory effect, not abolished by 5-HT1B or 5-HT1D antagonists, led to the conclusion that naratriptan has 5-HT1F-mimetic activity [89]. The authors of another in vitro study took the view that sumatriptan inhibited potassium chloride-induced CGRP release in isolated rat DM via 5-HT1D and 5-HT1F receptors [9]. Work reported by Hoskin et al. provided grounds for the suggestion that 5HT1F receptors were involved in the naratriptan- and eletriptan-induced inhibition of neuron activity in the solitary tract nucleus, though this was not tested by neurochemical analysis [115].

Ditans. Data on the weak agonistic activity of triptans in relation to 5-HT1F receptors [55, 186, 223] and our understanding of the role of these receptors in the functioning of the TVS [15, 45, 87, 89, 159] prompted development of a new class of serotoninergic drugs for relief of migraine attacks, i.e., selective 5-HT1F receptor agonists (SSOFRA – Selective Serotonin One F Receptor Agonists, or "ditans"), of which the best known are substances with codenames LY-334370, LY-344864, and COL-144 (LY-573144), also known as lasmiditan. Unlike triptans, the lasmiditan molecule does not have an indole core and is a pyridinoyl-piperidine with affinity for 5-HT1F receptors some 450 times greater than that for the 5-HT1B/1D subtypes [46, 166, 186]. On the basis of results from two randomized controlled trials, the US Food and Drug Administration (FDA) approved lasmiditan on October 11, 2019 under the trade name "Reyvow" as an oral treatment for the relief of migraine with and without aura in adults [241]. Lasmiditan received a marketing authorization in the European Union on August 17, 2022, [244]; as of March 2023, the drug remains unregistered in Russia. Post-marketing studies of lasmiditan confirmed its efficacy and safety in abortive antimigraine therapy and allow this drug to be regarded as a valuable alternative not only to triptans [181, 228], but also to gepants – as mentioned above, these are members of a new class of drugs with a specific action consisting of blockade of CGRP receptors [17, 177].

As lasmiditan is a 5-HT1F-mimetic, it is of note that subtype 1F metabotropic Gi/Go-protein-bound serotonin receptors are located in the STN, the TG, the walls of cerebral and extracranial vessels, and various supraspinal CNS formations, including the cortex, raphe nuclei, locus coeruleus, hypothalamus, etc. [2, 9, 15, 46, 87, 186, 222, 223]. The presynaptic location of these receptors within the trigeminal system was discussed; this is similar to the 5-HT1D subtype, though they are located predominantly on the central processes of TG cells [148]. Furthermore, recent data from immunohistochemical studies in rats have indicated minor

levels of expression of 5HT1F receptors on TG neurons, at least in comparison with the 5-HT1B/1D subtypes [73].

Pharmacodynamics: direct vasotropic effect. Despite the presence of 5HT1F receptors in the vascular wall [15, 46], a number of studies have particularly emphasized the complete absence of any vasoconstrictor effect on activation by lasmiditan [166, 185, 186, 226]. In particular, unlike sumatriptan, lasmiditan did not induce contraction of isolated human coronary, middle meningeal, or internal mammary arteries [185], nor did it provoke contraction of rabbit saphenous vein [166]. Lasmiditan did not affect the diameter of the common carotid or left circumflex coronary arteries in dogs or blood flow with them [185]. Other 5HT1F agonists displayed similar properties in earlier studies: LY-334370 did not produce ex vivo constriction of human cerebral arteries [196] or rabbit saphenous vein [48, 126] and LY344864 did not change carotid blood flow in cats [89], did not exhibit venoconstrictor properties [47, 48], and did not provoke contraction of isolated human or bovine cerebral arteries [29]. In this regard, lasmiditan is believed to have an advantage over triptans in not having a coronary constrictor effect, which generates optimism for its widespread use, including in patients with cardiovascular risks [13, 182, 185, 186, 223].

Pharmacodynamics: neurotropic action. The neuronal mechanism of the antimigraine action of lasmiditan is generally similar to that of triptans and consists of presynaptic blockade of the release of neurotransmitters from the peripheral and central terminals of the trigeminal nerve; considering the high lipophilicity of the drug, there is active discussion of the presence of its targets in the presumptively migraine-related structures of the CNS [169], where it could inhibit the conduction of the nociceptive stream via pre- and postsynaptic inhibition [46, 186].

On the basis of results from in vivo and ex vivo preclinical studies, it is known that:

– oral lasmiditan in rodents inhibited the extravasation of plasma proteins into the DM and the expression of c-fos proteins in the TCC on electrical stimulation of the TG [166]. Previous work showed that other 5-HT1F agonists displayed similar activity [159]: LY-344864 reduced c-fos immunoreactivity in the TCC on stimulation by intracisternal injection of capsaicin in rats [157] and mice [158]; LY-334370, LY-302148, LY-306258 [126], and LY-344864 [175] suppressed the increase in the penetration of plasma proteins into the DM provoked by electrical stimulation of the TG in guinea pigs;

– i.v. lasmiditan inhibited the background activity of TCC neurons and their Aδ-responses to electrical stimulation not only of the DM, but also the superior salivatory nucleus, i.e., it inhibited parasympathetically mediated activation of the TVS, which the authors felt gave a positive expectation that it would be effective in trigeminal autonomic cephalgias, particularly CHA [222]. Previous experiments showed that the 5HT1F agonist LY-344864 also suppressed the responses of TCC neurons induced by electrical stimulation of the DM in rats [196] and cats [89];

– lasmiditan suppressed KCl-induced CGRP release in isolated mouse DM, TG, and STN [137], as well as in the DM and TG in rat head hemisphere preparations [73]. A recent study found that the effect of lasmiditan was partially suppressed by the 5-HT1B/1D antagonist GR127935, which led the authors to the conclusion that it has the properties of a partial agonist of 5HT1B/1D receptors, at least at the level of the peripheral formations of the trigeminal nerve in rats [73]. Similar experiments had previously demonstrated that another 5HT1F agonist, LY-344864, suppressed CGRP release only in the DM [9];

– lasmiditan inhibited the dilation of meningeal arteries in rats induced by electrical stimulation of trigeminal afferents or i.v. capsaicin, but not CGRP, the effect being comparable with that of sumatriptan, pointing to inhibition of the release of vasoactive mediators from the terminals of trigeminal afferents by the mechanism of presynaptic inhibition at neurovascular synapses [137]. Earlier studies in rats showed that the 5HT1F agonist LY334370 did not suppress neurogenic dural vasodilation [196, 230];

– studies in a rat model of neuropathic pain induced by ligation of the sciatic nerve showed that lasmitidan reduced the severity of mechanical allodynia; the authors took view that this resulted from suppression of the neuroinflammatory response and enhancement of mitochondrial biogenesis (MB) mediated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [234]. Although the methodology used in these studies addressed extratrigeminal nociception, the results complement our understanding of the neurophysiological aspects of the pharmacodynamics of lasmiditan, especially taking account of the view that mitochondrial dysfunction may play a role in the pathogenesis of migraine [26, 62, 211]. It is of note that considerable effort has been put into studies of MB induction by ligand binding to 5-HT1F receptors. In particular, LY344864 was found to have a positive effect on MB in intact and damaged mouse spinal cord, apparent as an increase in the expression of mitochondrial DNA and mRNA for PGC-1α, a reduction in the volume of tissue damage, restoration of the integrity of blood vessels and the blood–spinal cord barrier, and improvement in motor function [202]; the same scientific group obtained similar results for lasmiditan a year later [203].

In vitro, LY344864 and LY334370 enhanced MB in renal proximal tubules, renal cortex, heart, and liver cells in mice, while in vivo, LY344864 accelerated the recovery of renal function after acute injury caused by ischemia/reperfusion [83]. In a similar model, lasmiditan also induced MB, restored vascular permeability, inhibited fibrosis, reduced proximal tubule damage, and reduced plasma creatinine levels [120]. LY344864 and lasmiditan enhanced MB in human and mouse glomerular endothelial cells in vitro [68]. Studies of the effect of LY344864 on rabbit proximal renal

tubule cells found that 5HT1F-mediated induction of MB could be mediated by a variety of intracellular mediators, forming two synergistic biochemical pathways [86].

All these data indicate that 5HT1F agonists have neuro- and nephroprotective properties, which in the future, subject to further accumulation of information on this topic, may contribute to the repositioning of lasmiditan and expansion of indications for its use, for example, for the treatment of neuropathic pain or renal failure. The situation is somewhat reminiscent of that with triptans, preclinical studies of which showed them to have a number of potentially therapeutic qualities in the "beyond migraine" concept, as described in detail above. In addition – and here, too, an analogy can be drawn with triptans in terms of their being presented as analgesics exclusively for migraine [36, 53, 138] – previous studies showed that LY334370 did not affect hyperalgesia in rats induced by injection of carrageenan into the paw, just as it had no effect on nociceptive reflex reactions in decerebrate rabbits, which led the authors to the conclusion that this drug had no systemic analgesic properties [196].

5HT1D Receptor Agonists. Concluding the review of 5-HT1-mimetics as abortive treatments for migraine, we cannot fail to mention that the selective 5HT1D receptor agonists PNU-109291 and PNU-142633 were at one time also seen as a non-vasoconstrictor alternative to triptans. Studies in animals showed that both drugs suppressed the extravasation of plasma proteins into the DM induced by electrical stimulation of the TG [54, 154]. In addition, PNU-109291 reduced capsaicin-induced c-fos reactivity in the TCC [54] and did not exhibit any vasoconstrictor effect in vitro [21, 29]. In turn, PNU-142633 blocked neurogenic dural vasodilation [230], significantly reduced the local increase in blood flow in the TCC caused by stimulation of the TG [154], did not affect blood flow in the internal carotid artery [43] or the common carotid or meningeal arteries [154], produced relaxation of isolated coronary artery [154], and inhibited CGRP release in the STN [9]. Unfortunately, despite these positive results, PNU-142633 was clinically ineffective as a treatment for migraine attacks [13, 94]. At the same time, the current literature contains views regarding the need for further investigation of the anti-migraine potential of 5HT1D-agonists [73].

Ergot Alkaloids. Dihydroergotamine (DHE) is an anti-migraine drug with a specific effect which was been used in clinical practice since the mid-40s [23, 200] and is still used in the USA, Europe, and Canada to relieve migraine attacks and CHA, though as of March 2023 it remains unregistered in Russia. Oral DHE has extremely low (less than 1%) bioavailability [23, 201], so is used as formulations for injection (D.H.E. 45) and intranasal administration (Migranal, Trudhesa) [237]. Alternative methods of delivering DHE, including inhalation, to improve its pharmacokinetic characteristics, efficacy, and tolerability are under active investigation [49, 201]. The chemical structure of DHE is similar to that of monoamine neurotransmitters, which accounts for its multitarget pharmacodynamics [23, 191], i.e., it has the ability to bind to the receptors for a multitude of different neurotransmitter systems, though it is primarily seen as a serotoninergic agent [237, 238]. Some slightly different data suggest that DHE is an agonist of all 5-HT1-receptor subtypes (the primary target is the 5-HT1D subtype), a 5-HT2-mimetic, and an antagonist of 5-HT7-receptors, which, in combination with activity on α-adrenergic and D2-like dopamine receptors, provides a complex neuronal-vascular mechanism for its anticephalgic action [15, 23, 55, 191, 200, 201].

The chemical precursor of DHE, i.e., the ergot alkaloid ergotamine, has been used as an abortive drug for migraine since the mid-20s and has a receptor profile of pharmacological activity similar to that of DHE [200, 191, 55, 185, 201, 239, 240]. Ergotamine is registered in Russia as part of the caffeine-containing fixed combination formulations Coffetamin [243] and Nomigren [245] as tablets prescribed to relieve migraine attacks, though the Medical and Pharmaceutical Service WebApteka.RU (https://www.webapteka.ru) indicates that Nomigren is not on sale anywhere in the country and Coffetamin is available in only one pharmacy in St. Petersburg (accessed March 2023). Outside Russia, ergotamine is available as Ergomar sublingual tablets and as a component of a fixed combination with caffeine as Migergot rectal suppositories, and as Cafergot and Wigraine tablets for oral administration [167, 239].

Overall, the antimigraine pharmacodynamics of ergot alkaloids can be regarded as triptan-like and they can be positioned as non-selective agonists of 5-HT1 receptors [2]. However, while their (speaking primarily of DHE) efficacy is approximately equal to that of triptans, these drugs are inferior to triptans in terms of safety, which limits their use [23, 167, 213, 218]. The current Russian clinical guidelines for the treatment of migraine present information on ergotamine exclusively as a drug able to cause MOH [1], while non-Russian sources assign DHE the role of an alternative drug for the relief of triptan-refractory migraine attacks [125, 194, 201].

Pharmacodynamics: direct vasotropic effect. Ergot alkaloids are conventionally seen as powerful vasoconstrictors, and in the 1970s, when the so-called vascular theory of the pathogenesis of migraine dominated, this property was put at the forefront of explanations of their antimigraine activity [2]. As new concepts of the pathophysiology of this disease have emerged [2], the role of the vascular component in mediating the anticephalgic effect of ergotamine and DHE, as well as triptans, has become uncertain.

Many studies have addressed the vasomotor effects of ergot alkaloids, primarily in ex vivo experiments on human and animal arteries and veins isolated from various anatomical sites, including the head; the vast majority of these pharmacological agents demonstrated the expected pressor effect [23, 55]. In particular, ergotamine induced constriction of the isolated human superficial temporal artery, which

was resistant to attempts to wash out the drug to terminate its action [173]. Both ergot alkaloids had contractile effects on isolated bovine middle cerebral artery, comparable in extent to those of triptans [184]. Both ergotamine and DHE produced significant contractions in human coronary arteries in vitro, these persisting even after repeated washout from the biological material, a procedure which rapidly reversed the vasoconstrictor effects of triptans [146]. DHE exhibited a contractile effect in relation to isolated rabbit saphenous vein, the extent of which was comparable with that of naratriptan and less than half the similar effects of sumatriptan and zolmitriptan [126]. In turn, the venoconstrictor effect of ergotamine in the same experimental conditions was 300 times more powerful than that sumatriptan and its mediation involved α1-adrenergic and 5-HT1B/1D receptors [48]. Experiments on vagosympathectomized dogs showed that both ergot alkaloids caused dose-dependent decreases in blood flow in the external carotid artery, mediated mainly by activation of 5-HT1B and α2A/2C-adrenergic receptors [216, 224, 225], though α1A/1B/1D adrenoceptors play an important role in the systemic vasopressor effect of ergotamine [227]. Overall, while they have approximately equal activity in terms of venoconstriction, ergotamine is regarded as a more potent arterioconstrictor [23, 191].

At the same time, single-photon emission computed tomography studies showed that neither ergotamine nor DHE, given i.v. to healthy volunteers, altered cerebral blood flow and neither affected positive cerebral blood flow reactions in the acetazolamide test [10]. Like sumatriptan, the two alkaloids did not impair shunting via dural arteriovenous anastomoses in pigs [63]. Doppler measurements indicated that ergotamine, like sumatriptan, does not alter blood flow velocity in the middle cerebral or basilar arteries in people with migraine [64].

Pharmacodynamics: neurotropic effect. As aseptic neurogenic meningovasculitis was widely seen as the cause of migraine attacks in the 1980s–1990s, many studies at that time addressed the effects of ergot alkaloids on the permeability of meningeal vessels. Overall, numerous experiments in rodents showed that i.v. DHE and ergotamine prevented extravasation of plasma proteins into the DM (but not into extracranial tissues) induced by electrical stimulation of the TG and/or i.v. capsaicin but not SP [37, 38, 126, 150, 187].

Like sumatriptan, i.v. infusion of DHE in rats produced 5-HT1B/1D-dependent blockade of the increase in blood CGRP in the superior sagittal sinus [34], dural mast cell degranulation, activation of endothelial cells, and platelet aggregation in postcapillary venules of the DM all occurring in response to electrical stimulation of the TG [35, 37]. Studies in cats using laser Doppler flowmetry showed that DHE, like sumatriptan, reduced the increase in cerebral (strictly speaking, meningeal) microcirculation in response to electrical stimulation of the TG, this occurring in parallel with a decrease in the blood CGRP level in the external jugular vein on the side of ganglion stimulation [90].

Intrathecal (level C1–C3) DHE inhibited the dilatation of the external carotid artery induced by intracarotid infusion of capsaicin, but not α-CGRP or acetylcholine, in vagosympathectomized dogs. This effect was canceled by the 5-HT1B/1D antagonist GR127935 and the α2-adrenergic blocker rauwolscine, indicating involvement of these receptors in its occurrence, and while the authors were unable to provide a clear explanation of the mechanism [149], it can be suggested that capsaicin provokes release of vasodilating mediators from perivascular nerve endings and that DHE prevents this process. Later studies using the so-called "pithed rat model" showed that DHE had a similar effect, suppressing vasodepressor CGRP-ergic mediation induced by spinal electrical stimulation (level T9–T12), which the authors believed was due to activation of presynaptic α2-adrenergic and 5-HT1B/1D receptors [95]. However, taking into account the facts that the vasodilatory response was assessed in terms of diastolic blood pressure rather than in the cranial arteries and that the plasma CGRP concentration was not monitored, it is difficult to see that the method used relates to modeling of migraine.

Electrophysiological experiments in cats showed that i.v. DHE suppressed the spike responses of TCC neurons to electrical stimulation of the superior sagittal sinus [114]. Studies in rats showed that i.v. DHE partially prevented c-fos expression in the STN, but not in the solitary tract nucleus, induced by introduction of autologous blood into the cisterna magna [170], while in cats, DHE blocked the accumulation of this neuron activation marker in the superficial laminae of the TCC provoked by electrical stimulation of the DM [114]. Ergometrine maleate, which the authors used as a water-soluble substitute for ergotamine, and DHE, given into the ventral posteromedial nucleus of the rat thalamus by microiontophoresis, inhibited the electrical responses of neurons in this structure to local glutamate administration, which completely reproduced the effect of naratriptan [198].

Conclusions. Serotoninergic drugs continue to constitute the core of specific abortive therapy for migraine. The uniqueness of this group lies in the fact that it includes drugs whose pharmacological actions have different levels of selectivity: the chronologically "old" ergot alkaloids, the well-studied triptans with more than 30 years of clinical use, and the relatively new lasmiditan still with little experience in use in real practice. The development of innovative dosage forms and delivery methods for known drugs contributes to increases in their efficacies and safety, along with a renaissance of interest even in dihydroergotamine, which at first sight seems to belong to the past. Members of all of the pharmacological classes listed here have similar mechanisms mediating their anti-migraine potential, neurotropic activity predominating over direct interference with vascular tone. It is entirely clear that further progress in the pharmacotherapy of migraine will not occur without new basic and applied research in experimental cephalgology, including research into serotoninergic drugs.

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